REMARKS

Claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202 were previously withdrawn from this application. Claims 127, 128, 152, 153, 178-182, 186, 188, 192-196, 199 and 203-204 were previously cancelled. Claims 119, 124, 170 and 205 are currently cancelled. Applicants reserve the right to file continuation or divisional applications directed to the cancelled or withdrawn subject matter. Claims 1, 11, 43, 44, 45, 54, 59, 60, 97, 120 and 125 are currently amended. Support for the amendments can be found throughout the specification, specifically in the claims as originally filed. No new matter has been added. Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-169, 184 and 191 are currently pending.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are rejected under 35 U.S.C. §112, first paragraph as failing to satisfy the enablement requirement. The Examiner states that while the specification is enabling for modulation of an immune response related to hepatitis, it is not enabling for treatment of any disease associated with an inflammatory response. Office Action page 2. Applicants respectfully traverse the rejection and assert that the claims are fully enabled as written. However, solely in an effort to further prosecution, independent claims 1, 11, 43, 44, 45, 54, 59, 60 and 97 have been amended to recite "wherein the pathogenesis of the disease is derived from an inflammatory immune response." The claims now recite the causation of the disease--the pathogenesis is caused by an inflammatory immune response. For the reasons previously discussed and those provided below, Applicants contend that the claims are enabled.

Applicants previously stated that limiting the claims to a disease associated with an inflammatory immune response "limits the particular diseases that would be used in the current invention since many diseases do not involve an inflammatory immune response and for most diseases that do involve an inflammatory immune response, this response is part of the curative process rather than the pathogenesis." Applicants are then invited to provide references which

teach that many diseases do not involve an inflammatory response. See Office Action page 3. It should be noted that the quotation from the previous response was in itself a response to a statement in the Office Action dated March 19, 2008. Specifically, the Examiner noted that "it is **absolutely** untrue that many diseases do not involve an inflammatory response" (emphasis added by Applicants). In our previous response, Applicants had offered an extensive list of diseases that Applicants have described as not involving inflammatory responses. However, without acknowledging the list of diseases itself, the Examiner repeats this request. Applicants respectfully assert that the list of diseases provided are known to those of skill in the art as lacking inflammation as part of their effects. It appears that the Examiner is requesting Applicants to prove a negative, which is often either difficult or impossible to do. Although Applicants believe that the list furnished in the previous response should be sufficient unless proven to be incorrect, Applicants are making an effort to provide some evidence for a lack of an obligatory connection between diseases and inflammatory responses. Thus, a Google search on May 27, 2009 with the term "non-inflammatory diseases" resulted in 2,020 references and a search with "noninflammatory diseases" resulted in 1,810 "hits". The following titles/passages are provided as an exemplary sample of the search:

In Wiederkehr et al., 1985 Clin Chem 31; 1537-1542

The abstract includes the following:

> The series included non-inflammatory diseases such as epilepsy, amyotrophic lateral sclerosis, and polyneuropathy; and inflammatory diseases such as multiple sclerosis and neurolues.

Gallo et al., 1989 J Neurol Sci 94; 241-253

The abstract describes patient populations that include:

> …17 patients with other inflammatory neurological disorders and 17 patients with other non-inflammatory neurological disorders.

Zaffaroni et al., 1991 J Neurol 238; 209-211

This paper is entitled: "CD4+ lymphocyte subsets in the cerebrospinal fluid of multiple sclerosis and non-inflammatory neurological diseases"

Ren et al., 1998 Clin Endrocrin & Metbolism 83; 1275-1283

Experimental results were summarized as follows:

> LIF detection rates were 69% in acute inflammatory diseases, 83% in chronic inflammatory diseases, 61% in noninflammatory disease…

Coe et al., 2001 J Inf Dis 183; 185-191

The abstract includes the following:

> Transmissible spongiform encephalopathies (TSEs) are initiated by a novel kind of agent that produces characteristic degenerative changes in the brain without a detectable systemic inflammatory response or serological changes.

Later in the same article:

> TSEs are generally regarded as noninflammatory diseases because of their afebrile clinical courses and the absence of detectable changes in the blood…

Hara et al., 1998 Am J Nephrol 18; 35-41

The abstract includes the following:

> Urine podocytes were absent in normal control, nonglomerular diseases such as urinary tract infection and nonglomerular hematuria, and glomerular, noninflammatory diseases such as minimal change nephritic syndrome and membranous nephropathy.

Sellebjerg et al., 2002 Scand J Immunol 56 101-107:

A description of the experimental methods includes the following:

> The control group consisted of 58 patients with noninflammatory disease (21 with spinal disc herniation, 10 with spinal stenosis, 10 with back pain…

Vartazaryan et al. 2009 Archiv Patol 67; 37-40

The Abstract describes different forms of chronic endometritis as:

> 2) a form associated with inflammatory pathology of other parts of the genital tract, 3) a form associated with non-inflammatory diseases of

the corpus and cervix of the uterus.

The above citations provide evidence that those skilled in the art have an appreciation which contradicts the position stated by the Examiner that "it is **absolutely** untrue that many diseases do not involve an inflammatory response." (Emphasis again added by Applicants). In addition, Applicants respectfully assert that one of skill in the art would recognize, as evidenced by the above articles, that numerous genetic diseases exist which do not involve immune responses. A number of such diseases were listed as examples of non-inflammatory diseases in Applicants' previous response. It is impossible to describe all diseases as involving an inflammatory response. There is no absolute correlation between diseases and immune response. As described previously, the currently amended claims are not directed towards diseases that lack an inflammation response. Instead, the claims are presently limited to a discrete subclass of diseases that involve an inflammation response that is part of the pathology of the disease (rather than serving as a curative process). As noted on page 4 of Applicants' previously submitted response: "As such, the nature of the diseases encompassed by the present claims are not simply those that they are 'associated' with an immune response, but more explicitly this association is in terms of those diseases where the immune response is part of the disease process rather than the disease cure." Thus Applicants respectfully reemphasize that the characterization of a diseases "associated" with an immune response is oversimplified and will be discussed further on.

The Examiner takes issue with Applicants' statement that differential diseases "share the common feature of an inflammatory process responsible for the symptoms of the disease," and invites Applicants to provide further elucidation and support in the specification. See Office Action page 3. Applicants respectfully submit that this subject was addressed in detail in the previously submitted Response at pages 5-6. It does not appear that the Examiner has acknowledged these statements. Applicants explained previously that this "common feature" is the fact that the diseases of the present invention derive all or part of their pathology from the immune response of the subject. The Examiner further cites to a passage from the specification (regarding cytokines) and then concludes "....cytokine production is not a common ground." See Office Action page 4. Applicants assert that a disease with the features of induction of

cytokine production resulting in greater harmful effects than beneficial results would display this "common ground." In addition, Applicants' previously described a shift in cytokine production as a consequence of treatment, not a description of a characteristic of a disease that required treatment.

It appears that the Examiner is dismissing the limitation that provides a "common ground" while at the same time concluding that there is no "common ground." As noted above, the presently pending application is a continuation-in-part of U.S. Patent Application Serial No. 10/375,906 (hereinafter the "parent application"), filed on February 27, 2003 (which has been incorporated by reference). This specification describes the administration of intermediary metabolites for treatment of immune mediated or immune related disorders as well as for other diseases (such as infectious diseases, metabolic diseases and cancer). The presently amended claims are directed to only one subset of these diseases, immune mediated or immune related disorders. A more definitive understanding of immune mediated or related diseases may be achieved through an analysis of the various diseases listed in originally filed claim 40, which are described as immune mediated or related. Each of the diseases listed in claim 40 represents a disease that may be caused by an immune reaction that contributes to the pathogenicity of the disease.

The Examiner states "The phrase, diseases with an inflammatory response, fails to described a limited group of diseases." However, the currently amended claims are limited to "diseases with an inflammatory response that contributes to the pathogenesis of the disease." As noted many times in Applicants' previous responses, the claims require inflammatory immune response which contributes to the disease process itself. One of skill in the art would recognize that this limitation is satisfied by a small number of diseases.

The Examiner states that there is no predictability in the field of art. Office Action page 4. The parent application predicted that the application of mammalian intermediary metabolites such as glycosylceramides would have beneficial effects on diseases which derive their pathology from the immune response of a subject. This fact was noted in Applicants' previous response. Applicants also previously described later-occurring experiments with three different model systems (each involving pathogenic immune responses) which showed alleviation of

disease symptoms upon treatment. Again, these studies were not directed towards any and all diseases, but rather a restricted subgroup that share the common feature of an immune response which contributes to or provides the pathogenic characteristics of the disease. Applicants have provided data showing three separate animal models (con A hepatitis model, an induced colitis model and a NASH model), distinctly dissimilar causation, which showed alleviation of symptoms after treatment with a beta-linked glycolipid.

The Examiner states that it would be unrealistic to "claim a method of treating any an all diseases associated with an inflammatory response." Office Action page 5. The Examiner then offers a list of diseases associated with inflammatory response. Applicants respectfully note that may of these diseases are characterized by the fact that an immune response is not part of the pathogencity of the disease process. For instance, Applicants are unaware of how induction of an immune response is part of the pathology of cancer and we are unaware of an immune response contributing to the pathology of heart disease. Pelvic inflammatory disease is a consequence of an infection that is sometimes seen as a consequence of a sexually transmitted disease. It may be a failure of the immune system to provide an adequate response to an infection, but the presence of the immune response does not contribute to development of disease in itself.

The claims are currently amended to recite "an inflammatory immune response contributes to the pathogenesis of the disease," thus limiting the claims to a specific subset of diseases. It appears that he Examiner is equating the "association" of an immune response as part of the disease manifestation but does not appreciate the requirement of the causative association, i.e., that the immune response generates the pathogenicity of the disease.

The Examiner states that "It would require years of further research to develop effective therapy for any and all diseases with an inflammatory response." See Office Action page 4. Applicants respectfully disagree. As detailed in the parent application, Applicants successfully designed appropriate experiments for providing relief from immune response generated pathogenic characteristics without any undue effort for the three different conditions described above.

The Examiner appears to be suggesting that there is likely to be some contribution

towards pathogenic effects derived from the immune response even in situations that are essentially beneficial curative processes; i.e. there is always a mixture of pathogenic and beneficial effects and it is only a question of the relative proportions of each. Office Action page 6. The Examiner cites to autoimmune disease as support that a curative process in the body may relate to pathogenesis. However, we do not believe that these are examples of a "mixed" situation. For instance, HBV infection and rheumatic heart disease are explicit examples where essentially no positive benefit is being derived for the subject and only pathogenic responses are being induced. These autoimmune disorders may be echoes of a previously beneficial response, such as the initial infection by HBV or streptomyces. However, a chronic autoimmune response against hepatic or heart tissues (respectively) would only generate pathogenic conditions. Applicants emphasize that the currently amended claims are directed not to the large number of diseases that do invoke an inflammatory response, but rather to a small subset of diseases where this invocation results in a pathological effect for the subject. Despite the fact that there may be some component in an inflammatory response (in general) that may contribute to what may be termed pathology, the small minor characteristics cited by the Examiner should not define the disease. For instance, wound healing may display be redness, swelling and soreness associated with the healing process; however, to one of ordinary skill in the art, these conditions would not be considered to be part of a pathology *per se* but an obvious sign of a curative process that will ultimately benefit the subject.

In conclusion, claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 clearly satisfy the enablement requirement. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(b)

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 97, 109, 119, 120, 124-126, 151, 157, 161-168, and 184 are rejected under 35 U.S.C. §102(b) as being anticipated by Liotta *et al.* (U.S. Patent No. 6,610,835, hereinafter "Liotta"). The Examiner states that Liotta describes the use of sphingolipid derivatives and their methods of use, including the treatment of inflammatory conditions. The Examiner further states that the compounds used in Liotta are suited for the

treatment of colitis. The Examiner then states that "The authors provide the same method steps comprising administering the same ingredient to the same population. Inherently, this would result in the same effects, including changes in cytokine responses, NKT cells or Th1/Th2 balance". Office Action pages 8-9.

In response to Applicants' previously submitted remarks, the Examiner states that the claims do not exclude the use of sphingolipids.

To support a rejection under Section 102, an Examiner must show that each and every element recited in the claimed invention is taught by a single reference. MPEP § 2131. Applicants continue to assert that the claims as written are novel over Liotta. However, solely in an effort to further prosecution, independent claims 1, 11, 43, 44, 45, 54, 59, 60 have been amended to recite "wherein said intermediary metabolite is a lipid or glycolipid", thus specifying the identity of the glycolipid.

Wit regard to Liotta, the Examiner states that "the metabolites are defined in the claim as only comprising a lipid or glycolipid." See Office Action page 6. The claims recite that a lipid or glycolipid is required to be a "mammalian intermediary metabolite". This is clearly described in the specification. For instance, under the heading of Field of the Invention, the specification states that "the invention relates to the use of a naturally occurring, mammalian intermediary metabolites…" In addition, the Summary section states "This invention relates to the use of a naturally occurring, mammalian intermediary metabolite..." and "This invention provides a process for treating a disease in a mammalian subject comprising administering to the subject an effective amount of a mammalian intermediary metabolite. In addition, the specification of the parent application defines an "intermediary metabolite" as follows: "In the present invention, metabolites or intermediary metabolites are considered to be products of enzymatic processes in a mammalian system." U.S. Patent Application Publication No. 20040171522, paragraph [0021].

Thus, the intermediary metabolites of the pending claims are included in the definition of the artificial synthetic creations of Liotta. As pointed out in Applicants' previous response, Liotta teaches that the non-synthetic intermediary metabolite forms of lipids and glycolipids were deemed inadequate for their described methods. Liotta requires artificial compounds. The

specification and claims of the present invention require that a glycolipid must be a mammalian intermediary metabolite. Liotta does not teach these types of non-synthetic intermediary metabolites and therefore does not teach each and every element of the pending claims. Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. §103(a)

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are rejected under 35 U.S.C. §103(a) as being obvious over Liotta, Makowska and Tanguchi *et al.* (EP 0988860; hereinafter "Tanguchi"). The Examiner states that while Liotta dos not teach the use of CD1 receptor presenting cells, glucosylceramide or galactosylceramide, or food depravation, Liotta does teach that sphingolipids are found in a number of foods. The Examiner then concludes that the invention as a whole is obvious. Office Action page 10. The Examiner then states that Makowska demonstrates the use of alpha-glucosylceramide in stimulating NKT cells (Vα14+). The Examiner then writes that Tanguchi teaches a method of treating disorders (including ulcerative colitis) through the use of glycosylceramides and derivatives for the activation of NKT cells. The Examiner then concludes that it would have been obvious to combine the teachings of Makowska and Tanguchi to perform a method of administering an intermediary metabolite with an antigen presenting cell. Office Action page 10-11.

Applicants respectfully traverse the rejection. As explained above, Liotta neither teaches nor discloses administration of non-synthetic intermediary metabolites. Liotta teaches analogues rather than natural products. This deficiency is not remedied by Tanguchi or Makowskii. Neither of these references would suggest that non-synthetic intermediary metabolites would be effective. The presently amended claims **are** limited to a specific conformation in the sense that they do not correspond to the alpha linked forms of Makowska as alpha linked glycolipids have never been found in a mammalian cell (see previous discussion of intermediary metabolites). Only the beta conformation is seen in mammalian cells. In its natural state, alpha glycolipids have only been isolated from a marine sponge. Taniguchi also describes only non-mammalian compounds (alpha-glycosylceramides). As noted above, the claims have been amended to

provide a clear and concise requirement that the lipids and glycolipids are required to be intermediary mammalian metabolites, in contrast to the artificial analogues described by Makowska and Taniguchi. The combination of Liotta, Makowska and Tanguchi does not result in Applicants' presently claimed invention A method for the treatment of a disease in a mammalian subject comprising administering to said subject an effective amount of a mammalian intermediary metabolite, wherein said intermediary metabolite is a lipid or glycolipid.

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are not rendered obvious by the combination of Liotta, Makowska and Tanguchi. Applicants respectfully request withdrawal of the rejection.

Double Patenting

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-15 of copending Application No. 11/378,941.

As this is a provisional rejection, Applicants respectfully request the rejection be held in abeyance until the finding of allowable subject matter.

Conclusion

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

The Examiner is invited to contact the undersigned at 412-918-1100 to discuss any matter concerning this application.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the deposit account number 50-0525.

Respectfully submitted,

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